# POOR LEGIBILITY

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date, or meperidine. She claims that withdrawal symptoms for any single drug do not occur. Multihabituation seems to be a way of life for these antisocial individuals.

The manufacturers of LSD-25 have exercised admirable restraint in not attempting to introduce the drug commercially until its psychologic and physiologic side effects are more precisely known. They carefully scrutinize applications for its use by investigators. It is distributed only for investigational use at this time.

Now that it has become available from sources concerned solely with the profits from illicit sales, physicians may encounter patients in a state of LSD-25 intoxication. A clinical laboratory test to detect this agent is not available. The diagnosis can generally be made from the history and interview, despite the bizarre and variable nature of the subjective effects. In the acute phase the pupils are widely dilated. Other symptoms of sympathetic stimulation may be present, for example, tremor, hyperreflexia, hypertension, and an elevated temperature. The visual distortions are characteristic: intensification of colors, mobile, multicolored hallucinations or pseudohallucinations, or the illusory undulation of fixed objects. With closed eyes flowing colored geometrical designs are seen. Synesthesias, hyperacusis, alterations of body image, aberrations of time sense, derealization, delusion and affectual changes ranging from elation to p may last for 4-8 hours when dosages exceed per kilogram. Doses of 20 mcg. per kilogram known to have been given without a lethal come, but the psychic disturbance becomes found. Complete loss of reality contact, total drawal, and dissolution of the ego boundaries described.

### Summary

The use of LSD-25 can be attended with ser complications. This is especially true now th blackmarket in the drug exists. The danger suicide, prolonged psychotic reactions, and social acting out behavior exist. Misuse of the alone or in combination with other agents ha encountered. Properly used, LSD-25 remain important investigational instrument which assist in the elucidation of significant problem the study of the mind.

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FEL n=1 at 450-600 mg/d

# Fatal Aplastic Anemia Following Use of Potassium Perchlorate in Thyrotoxicosis

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THIS IS A REPORT of a patient who died of aplastic anemia resulting from potassium perchlorate administered in the treatment of hyperthyroidism. Three similar cases have recently been reported in Great Britain.[1-3] The gravity of this complication, despite its rarity, precludes further therapeutic use of this drug except perhaps under unusual circumstances.

## Report of a Case

The patient was a married white woman. At her death on June 28, 1961, she was 26 years of age. At age 15, following a fall, she had mild nausea, vomiting, and headache for 3 weeks. During her only pregnancy, in 1958, she had an attack of pyelitis. For the past 6 years infrequent migraine headaches were noted, for which she occasionally took ergotamine. She had tonsillectomy at age 4, appendectomy at age 17, and dilatation and curettage of the uterus at 18 years of age.

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Hyperthyroidism began in late 1957 with symptoms of nervousness and weight loss. In May 1959, she was found to have a small goiter but no exophthalmos. The level of protein-bound iodine in the serum was 18 μg/100 ml. A biopsy of the thyroid gland was performed prior to the institution of therapy with potassium perchlorate; this was done as part of a study to determine the effect of the drug on the thyroid gland. Potassium perchlorate (0.5% in water) was given at a dose of 800 mg. daily. After one week the patient noted headache, nausea, slight fever, and mild chills. The medication was discontinued for 4 days and she felt better. Therapy at the previous dose was resumed; in a few days she noted itching of the skin, and a macular, faintly erythematous rash developed over the anterior part of the chest. The medication was again discontinued, and the rash promptly cleared. The drug was then given at a smaller dose of 600 mg. daily, and the patient appeared to tolerate it satisfactorily. She began to improve and gained 18 pounds, and within 2 months all symptoms of hyperthyroidism disappeared. She resumed work as a clerk. In early August, the dose of perchlorate was further reduced to 450 mg. daily.

In October, 1959, she noted moderate menstrual flow



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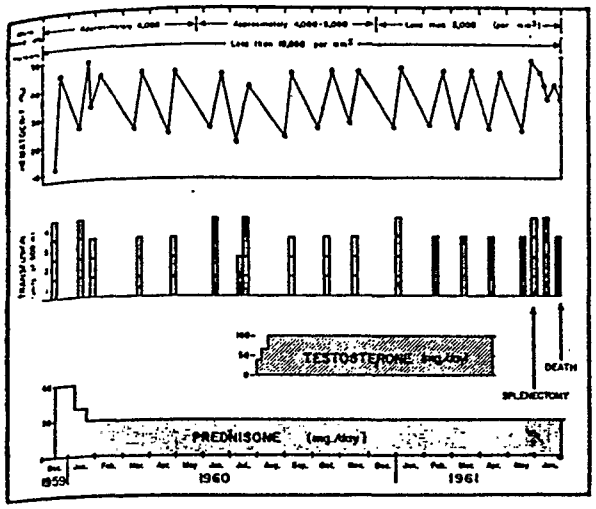
but considered this part of her general improvement, since her periods formerly were scanty. In November, however, menstrual bleeding was profuse; shortly thereafter she noted fatigue, exertional dyspnea, and occasional pounding headaches. A mild nosebleed occurred, and her legs bruised easily. She was admitted to the hospital in December. She




Findings and treatment in woman who died at age 26 of aplastic anemia following administration of potassium perchlorate.

appeared pale, and a few bruises were noted. The liver and spleen were not palpable. There was no jaundice. The hematocrit was 10.7%, and the white blood cell count was 6,100 cells per cubic millimeter, with the following differential count: juveniles 2.5%, segmented neutrophils 23.5%, eosinophils 0.5%, monocytes 3%, and lymphocytes 70.5%. There were 6,000 platelets per cubic millimeter. Three aspirates of bone marrow revealed no cells. The rate of incorporation of radioactive iron by red blood cells in vivo was 2% in 10 days (normal 70% to 80%), and the rate of disappearance (half-life) of radioactive iron from the plasma was 345 min. (normal 60 to 90 min.); the results of these studies established a defect in the production of red blood cells. The Coombs' test (indirect) was negative, the level of bilirubin in the serum was not increased, and the survival of radioactive chromium-labeled red cells was approximately normal, the time being 21 days (normal 25 to 35 days); these findings excluded significant hemolysis of red cells.

The diagnosis of aplastic anemia appeared likely. At the time, no other instances of this complication had been reported, and we were unable to learn of similar cases by corresponding with physicians who were known to us to use potassium perchlorate; nonetheless, we held the drug as suspect and immediately stopped administering it. The patient's subsequent course is depicted in the figure. She was given 4 transfusions of whole blood, 500 ml. each, and prednisone, 60 mg. daily. Her strength improved. After 3 weeks the dose of prednisone was reduced to 40 mg. daily.

In January, 1960, she again was anemic and received 3 transfusions, the hematocrit increasing from 24% to 46%. Facial changes of the Cushing type were noted, and the dose of prednisone was reduced to 30 mg. daily. Hyperthyroidism recurred. It appeared unwise to administer propylthiouracil or methimazole, and subtotal thyroidectomy was considered hazardous due to continuing severe thrombocytopenia. The treatment of choice appeared to be radioactive iodine, since only a small dose would be required to destroy the small amount of excess thyroid tissue. She was given 3.5 millicuries of $I^{131}$ and responded satisfactorily.

Her course over the next year was marked by repeated admissions for transfusions and by lack of any significant evidence of regeneration of bone marrow. Therapy with testosterone propionate in linguets was started in August; the dose was increased from 40 mg. to 100 mg. daily over a period of one month, and this dose was continued until May, 1961. During this therapy her menses ceased, her voice deepened, and she noted increased libido. There was no discernible effect on hematopoiesis.

Her requirement for transfusions of blood remained unchanged. The platelet level was always less than 10,000 per cubic millimeter. The number of white blood cells diminished gradually, reaching levels of approximately 2,000 cells per cubic millimeter; the differential count was essentially unchanged. Spontaneous bleeding into the skin and from mucous membranes became more severe. Frequent febrile reactions to transfusions were noted. A transfusion of fresh platelets failed to increase the number of platelets in the blood. Following cessation of therapy with testosterone propionate, menstrual bleeding recurred.

In June, 1961, splenectomy was performed without unusual difficulty; the spleen weighed 75 gm. and measured 9 × 5.3 × 3.2 cm. Grossly it appeared normal but microscopically it showed hemosiderin. The postoperative course was marked by slight fever, moderate hemorrhage into the wound, and steady deterioration of the patient's condition. Anemia was treated with multiple transfusions. Fresh subcutaneous and submucous hemorrhages and a brisk bloody diarrhea developed. On the 27th postoperative day she became unconscious, and breathing required mechanical support. She died on the 28th postoperative day.

Autopsy was done 3 hours after death. All tissues showed extensive hemorrhage. There were subdural, subarachnoid, and intracerebellar hemorrhages. Sternal and vertebral marrow was fatty. The liver and pancreas showed hemosiderosis. There was slight infection and hemorrhage at the site of splenectomy.

## Comment

The patient reported was a 26-year-old woman who died of aplastic anemia following the use of potassium perchlorate as treatment for thyrotoxicosis. Three similar cases have been reported in Great Britain,[1-3] and editorials [4,5] have called attention to the hazard of using this drug. This complication has not been reported as a consequence of a single dose of the drug used diagnostically to assess the degree of organification of iodine by the thyroid.

Potassium perchlorate ($KClO_4$) has a simple chemical structure and has been employed successfully in the treatment of hyperthyroidism for about 8 years.[6,7] It is generally considered as efficacious as propylthiouracil and methimazole, commonly used in the United States, and methylthiouracil and carbimazole, usually employed in Great Britain. Until recently it has been held to be relatively nontoxic. In collecting 818 published cases of patients with thyrotoxicosis treated with potassium perchlorate, Johnson and Moore [2] found 36 patients (4%) who showed toxic reactions. These were usually mild, consisting of gastric distress, skin rash, fever, lymphadenopathy, or neutropenia, and subsided promptly on cessation of treatment. Nonfatal neutropenia or agranulocytosis has been noted in 4

patients.[4] Reactions were more frequent when doses of potassium perchlorate exceeding 1 gm. daily were used.[6-8] Only 1 of the 4 patients who died of aplastic anemia received as much as 1 gm. daily, and this observation suggests that their marrow was uniquely sensitive to the drug.

Potassium perchlorate has been given to approximately 35 adult thyrotoxic patients at The Johns Hopkins Hospital. It has appeared to be especially of value in those patients who previously have shown sensitivity to propylthiouracil or methimazole or both drugs. Indeed, until this recent untoward reaction, we were beginning to hold potassium perchlorate as the antithyroid drug of choice.

In great Britain it has been suggested that those dispensing this drug be required to attach to the bottle a label warning of possible hematologic reaction and urging patients to report to their physicians promptly if an untoward response is detected.[1-3] It is not known, however, if this would prove worth while, since it may be that once aplasia is induced it is irreversible. In the patient reported by Johnson and Moore,[2] there was at the time of recognition of a reaction only a partial suppression of the white blood cell formation, although the marrow showed complete absence of nucleated red cells. The drug was immediately withdrawn, but agranulocytosis and severe thrombocytopenia later developed, and the patient died in 6 weeks. In our patient, the white blood cell count was normal when the drug was discontinued, but progressive leukopenia ensued.

Therapy with prednisone or prednisolone has been employed in all 4 cases of aplastic anemia due to potassium perchlorate. There is no evidence that these steroids proved either helpful or detrimental. In our patient, spontaneous hemorrhagic phenomena appeared to be partially suppressed when steroids were given, although there was no increase in the platelet count. A transfusion of fresh platelets was given but did not bring about an increase in their number; this refractoriness may have been due to the development of an iso-antibody to platelets resulting from earlier transfusions of whole blood. Teststerone propionate was also administered without apparent benefit, although marked androgenic effects resulted. In a recent review[9] on the management of aplastic anemia it was reported that splenectomy was followed by improvement in 4 of 15 patients. Our patient lived only 4 weeks after splenectomy, and during that period no beneficial effect was noted on the blood levels of red cells, white cells, or platelets.

## Conclusion

A 26-year-old woman received potassium perchlorate for hyperthyroidism. A dose of 600 mg. daily was given for 2 months and then reduced to 450 mg. as the patient showed improvement. Five months following initiation of therapy she had a moderately heavy menstrual period. This heralded the onset of bone-marrow failure but it went unrecognized. Therapy was continued for another month, at time she was severely anemic and drug was immediately discontinued. Studies of the blood, the bone marrow, and the rate of formation of red cells confirmed the clinical diagnosis of aplastic anemia. The patient was given prednisone, multiple and repeated transfusions, and testosterone propionate; finally, splenectomy was performed. Therapy was unavailing, and she died 18 months following discontinuance of potassium perchlorate.

This is the fourth recorded instance of fatal aplastic anemia secondary to the therapeutic use of potassium perchlorate for hyperthyroidism. The reaction appears to occur uncommonly among the large number of persons who have received the drug. Nonetheless, it is such an irreversible adverse response that further use of the drug in therapy appears unwise except under unusual circumstances.

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### Generic and Trade Names of Drugs

Propylthiouracil—*Propylthiouracil.*
Methimazole—*Tapazole.*
Testosterone proprionate—*Andronate, Andrusol-P, Masenone, Neo-Hombreol, Oreton Propionate, Perandren, Testosterone Propionate.*
Methylthiouracil—*Methiacil, Thimecil.*
Prednisone—*Deltasone, Deltra, Meticorten, Paracort, Prednisone.*
Prednisolone—*Delta Cortef, Hydeltra, Meticortelone, Meticorten, Derm, Paracortol, Prednisolone, Sterone, Sterolone.*

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